**ANTINEOPLASTIC DRUGS 2**

**Objectives and Questions Before Class**

* mech action methotrexate and major SE of purine analogs which affected by allopurinol
* which ATB cause pulmonary fibrosis what chemo drug is dextrazosan used to protect damage from? something like that
* which mitotic spindle drug causes periph neuropathy
* major metabolite 5 fluorouracil that causes RNA and DNA damage

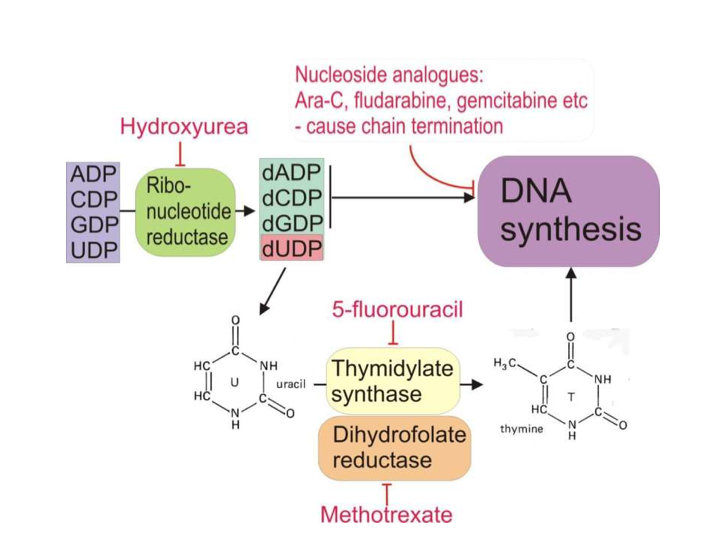
Objectives

* Describe the mechanism of action of various individual anticancer drugs under each class.
* Explain the bioactivation pathways required for the action of cyclophosphamide.
* Describe the intracellular activation pathways of different antimetabolites.
* Explain the use of antidote in high methotrexate therapy.
* List the major therapeutic indications of various anticancer drugs.

**ANTIMETABOLITE DRUGS**

* Designed to block DNA synthesis
  + Based on idea that cancer cells divide more rapidly than normal cells, so more vulnerable
* Originally considered to be cytostatic rather than cytotoxic, but now recognized that many produce cell death by triggering apoptosis
* Unlike most conventional chemotherapy drugs, development by rational synthesis rather than empirical screening for anticancer effects
* Most are either nucleoside analogues that interfere with DNA synthesis or block methylation of uracil to thymidylate

**ANTIMETABOLITE OVERVIEW**



* End point is to affect DNA synthesis
* most antimetabolites are S phase spec inhib
* 5FU can induce p53

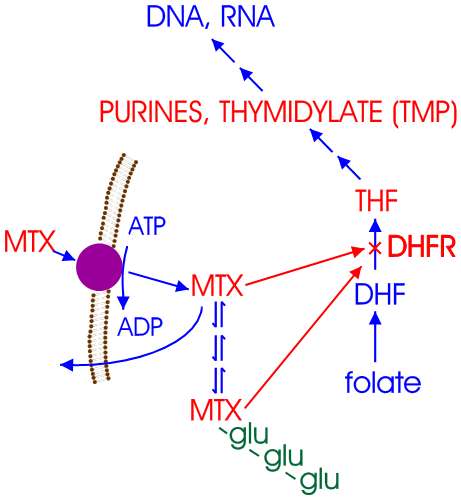
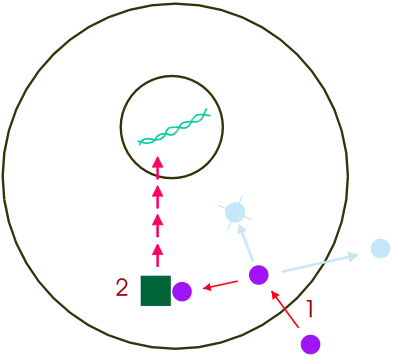
**ANTIMETABOLITES**

* **Folic acid analogs**
  + **Methotrexate**
* Pyrimidine analogs:
  + 5-Fluorouracil and 5-Fluorodeoxyuridine
  + *Deoxycytidine Analogs*:
    - Gemcitabine and Cytarabine
* Purine analogs:
  + 6-Mercaptopurine, Azathioprine
  + 6-Thioguanine

**ANTIFOLATES**

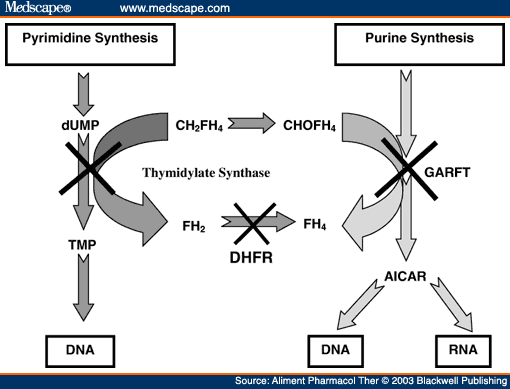
* **Antifolates** are drugs which impair the function of folic acids.
* Many are used in cancer chemotherapy, some are used as antibiotics or antiprotozoal agents.
  + for chemotherapy they use higher concentrations
* METHOTREXATE
* PEMETREXED

**METHOTREXATE (MTX)**

* MTX is administered by i.v., parenteral, or oral routes
* Used for treatment of breast cancer, head and neck cancer, bladder cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin’s lymphoma, choriocarcinoma
  + **Used to induce and sustain remission in acute lymphoblastic leukemia (ALL) in children.**
* Methotrexate anti-tumor activity is a result of the inhibition of folic acid reductase, leading to inhibition of DNA synthesis and inhibition of cellular replication.
* 
  + - * + sim structure, cause inhib of enzyme producing tetrahydrofolate
  + 
* Mechanism of action:
  + Blocks DNA synthesis through inhibition of the enzyme **dihydrofolate Reductase** (DHFR=Dihydrofolate Reductase)
* Methotrexate: A Folate Analog
  + Methotrexate (MTX) is taken up by the folate uptake system, and is converted to the polyglutamate form by the same enzyme that traps folate in cells as the polyglutamate.
    - can acumulate in liver, which can be bad
  + Methotrexate is a potent inhibitor of dihydrofolate reductase (DHFR), and shuts down production of tetrahydrofolate (THF),
    - a necessary precursor for production of purine bases and thymidylate.
  + the polyglutamate form of methotrexate is capable of inhibiting DHFR.
  + Large amounts of MTX polyglutamate can accumulate in cells, especially liver cells, as the result of accidental overdose or exposure of patients to high-dose MTX therapy.
  + trapped MTX can cause severe damage to normal cells by prolonged shutdown of THF production resulting in kidney & liver damage, severe mucositis (severe ulceration)
  + Leucovorin rescue
    - Administered by i.v. or orally
    - a form of THF that can readily be taken up by cells. If it is administered after overdosing with MTX
      * bc DHFR inhib
    - it can supply THF needed for cell survival until the MTX polyglutamate is finally broken down to free MTX and leaves the cell by diffusion.
    - With high-dose MTX and leucovorin rescue, the patient must be well-hydrated and urine alkalinized, or MTX will precipitate in acidic tubular fluid.
* MECHANISMS FOR DEVELOPMENT OF RESISTANCE TO METHOTREXATE
  + 

1. Decreased uptake, decreased folate carrier system.
2. Increased DHFR content or mutated DHFR that does not bind methotrexate well.

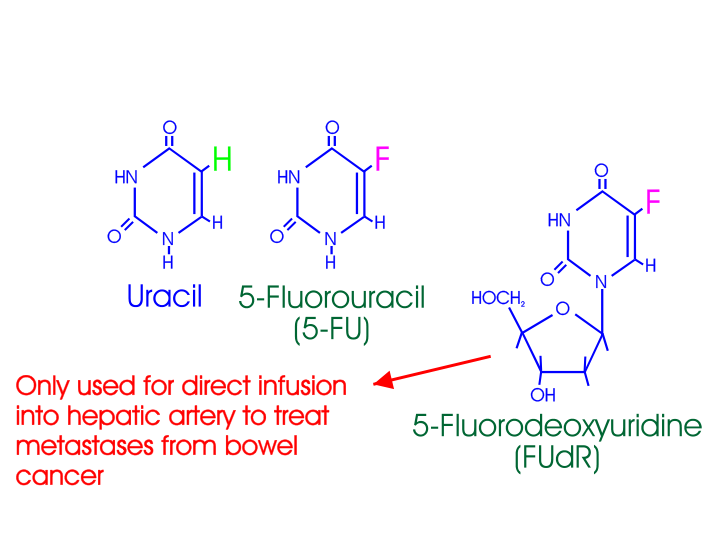
**PEMETREXED**

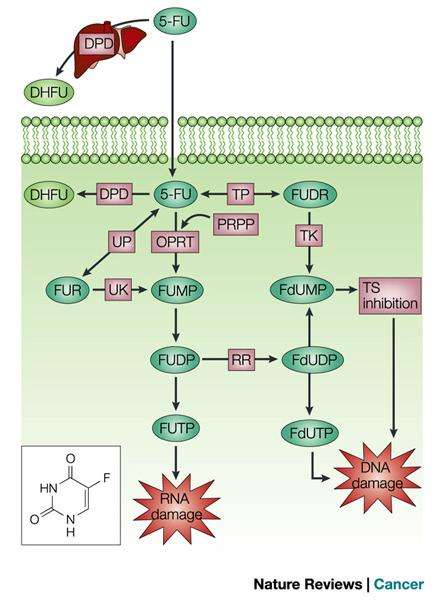
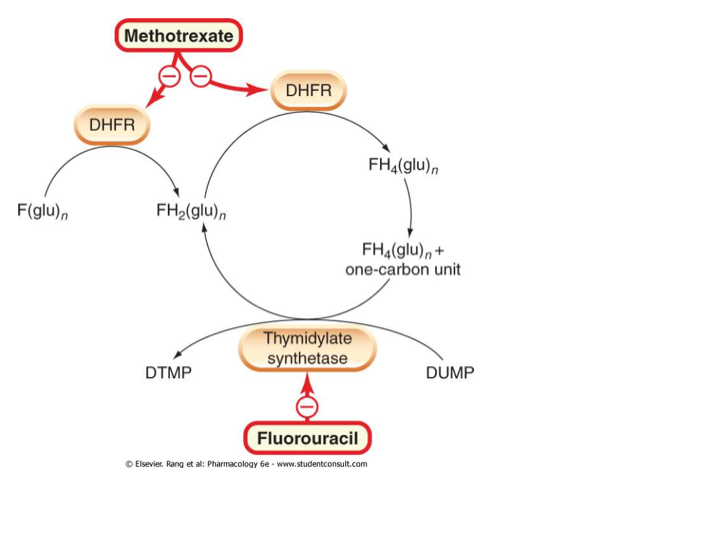
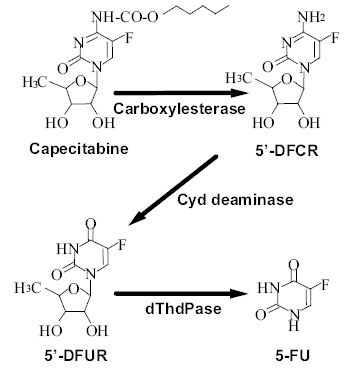
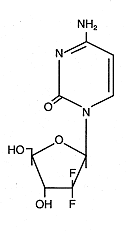
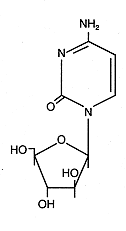
* Used for treatment of mesothelioma and non small-cell lung cancer
* an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting folate-dependent metabolic processes.
* MOA: works by inhibiting three enzymes used in purine and pyrimidine synthesis
  + thymidylate synthase (TS)
  + dihydrofolate reductase (DHFR),
  + and glycinamide ribonucleotide formyltransferase (GARFT)
* prevents the formation of DNA and RNA, which are required for the growth and survival of both normal cells and cancer cells.
  + larger spectrum so less resistance than MTX
* Patients are required to be on folic acid and vitamin B12 supplementation when they are on pemetrexed therapy
* 

**ANTIMETABOLITES**

* Folic acid analogs:
  + Methotrexate
* **Pyrimidine analogs:**
  + **5-Fluorouracil and 5-Fluorodeoxyuridine**
  + ***Deoxycytidine Analogs*:**
    - **Gemcitabine and Cytarabine**
* • Purine analogs:
  + 6-Mercaptopurine, Azathioprine
  + 6-Thioguanine

**PYRIMIDINE ANTIMETABOLITES -URACIL ANALOGS**

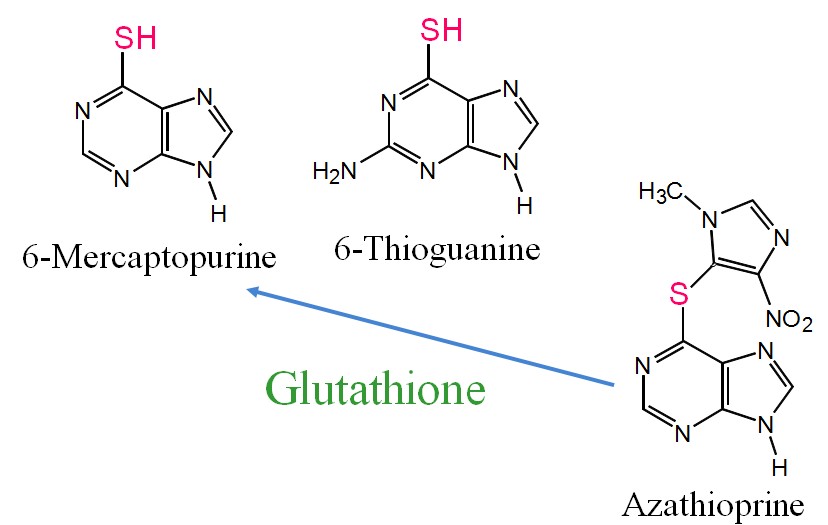
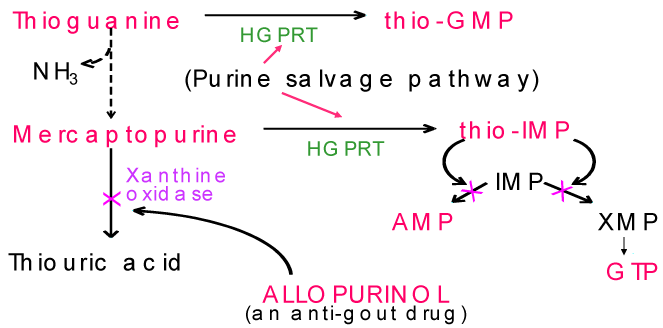


* **5-FLUOROURACIL**
  + 5-FU is the most widely used agent in the treatment of colorectal cancer
    - It also has activity against cancers of the breast, stomach, pancreas, esophagus, liver, head and neck, and anus
  + 5-FU is normally administered by i.v. or topical
  + 5-Fluorouracil (5-FU) is converted to three main active metabolites:
    - FdUMP - fluorodeoxyuridine monophosphate
    - FdUTP - fluorodeoxyuridine triphosphate
    - FUTP - fluorouridine triphosphate
  + The main mechanism of 5-FU activation is conversion to fluorouridine monophosphate (FUMP)
  + FUMP is then phosphorylated to fluorouridine diphosphate (FUDP)
    - which can be either further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP) for RNA damage
    - or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR) for
    - FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP for DNA damage
  + **The actions of methotrexate and fluorouracil are synergistic**
    - 
* **CAPECITABINE**
  + used in the treatment of metastatic breast and colorectal cancers.
  + used alone as an adjuvant therapy following the complete resection of primary tumor in patients with stage III colon cancer
  + It is an orally administered systemic prodrug that has little pharmacologic activity until it is converted to 5-FU by enzymes that are expressed in higher concentrations in many tumors.
  + 
    - carboxylesterase in liver
    - Cyd deaminase is in most tissues
    - DthdPase is high in some cancers so more specific and less SEs
  + MOA:
    - In the liver, carboxylesterase hydrolyzes  much of the compound to 5'-DFCR (5'- deoxy-5-fluorocytidine).
    - Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-DFUR.
    - The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU.
    - Some human carcinomas express higher  thymidine phosphorylase concentrations than surrounding normal tissues.
  + Adverse effects
    - In some cases hand-foot syndrome may occur (10-50%of the patients)
      * Tingling, burning, or numbness
      * Redness or swelling
      * Flaking or peeling skin
        + can interfere w/ finger prints
      * Small blisters
      * Sores or breaks in the skin
      * Discomfort or pain
    - Interruption in the treatment and dose reductions are very frequent due to this toxicity.
* **GEMCITABINE**
  + Inhibits ribonucleotide reductase, and is incorporated into DNA leading to chain termination
  + First line drug for pancreatic cancer; also used in treatment of lung and bladder cancers.
  + 
* **CYTARABINE (Ara-C)**
*  
  + Limited to hematogolic malignancies
  + Used for treatment of acute myelogenous leukemia and non-Hodgkin’s lymphoma
  + Antimetabolie that is converted by deoxycytidine kinase to 5’ mononucleotide (ara-CMP)
  + Ara-CMP is further metabolized to the main cytotoxic metabolite ara-CTP
  + acts through direct DNA damage and incorporation into DNA. Blocking the progression of cells from the G1 phase to the S- phase.

**ANTIMETABOLITES**

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**PURINE ANALOGS**

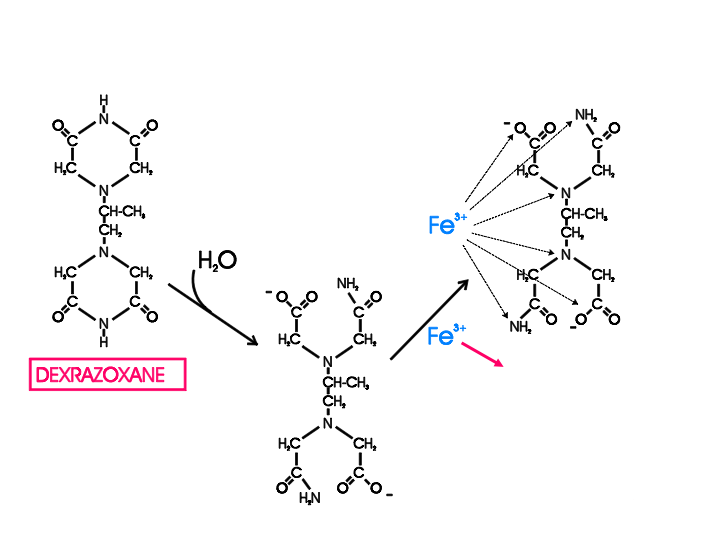
* **AZATHIOPRINE**
  + Azathioprine is rarely used to  treat cancer, it is mostly used as  an immunosuppressant.
    - for gout and rheumatoid arthritis
  + It is a pro-drug, converted in the body to the active metabolite 6-mercaptopurine.
  + MOA: drug metabolism results in the incorporation of thiopurine analogues into the DNA structure, causing chain termination and cytotoxicity.
    - 
* **6-MERCAPTOPURINE 6-MP**
  + First of the thiopurine analogs found to be effective in cancer therapy.
  + Used for mostly treatment of childhood acute myeloid leukemia (AML)
  + Mercaptopurine interferes with nucleotide interconversion.
* **6-THIOGUANINE (6-TG)**
  + sim to 6-MP
  + Acute lymphoblastic leukemia
  + Acute myelogenous leukemia
  + 6-TG has **synergistic** action when used with **cytarabine** in the treatment of adult acute leukemia
  + Thioguanine inhibits purine biosynthesis and is incorporated into the DNA
  + 6-TG is closely related to 6-MP, both in structure and in metabolism.
* **PURINE ANALOG ANTAGONISTS**
  + 
    - Thioguanine and mercaptopurine are inactive in their parent form and must be metabolized by HGPRT (hypoxanthine-guanine phophoribosyl transferase) to form the monophosphate nucleotide 6-thioinosinic acid
    - The monophosphate form is eventually metabolized to the triphosphate form and incorporated into both RNA and DNA.
    - Thioguanine and mercaptopurine inhibit synthesis of purine nucleotides necessary for RNA and DNA synthesis
    - A key distinction is **the drug interaction between mercaptopurine and allopurinol, a drug used to treat gout.**
    - There is no interaction between thioguanine and allopurinol.
      * if a pt is taking antigout allopurinol and give purine analog, which would be affected? eg of test q
    - Allopurinol inhibits the enzyme xanthine oxidase, which is responsible for formation of urate from purines.
    - Recall that one of the common adverse effects of antineoplastic drugs is the generation of large amounts of uric acid upon first treatment with the anticancer drugs.
    - Often, patients who receive mercaptopurine must be treated with allopurinol to prevent gout. In this case, the dose of mercaptopurine must be reduced by more than one-half, because of allopurinol’s inhibition of mercaptopurine biotransformation.

ANTIBIOTICS AND ALKALOIDS

* Antibiotics
  + Doxorubicin
  + Dactinomycin
  + Bleomycin
* Mitotic spindle poisons
  + Vinca alkaloids, Vinblastine and Vincristine
  + Paclitaxel (Taxol)
* Epipodophyllotoxins
  + Etoposide
* Camptothecins
  + Topotecan and Irinotecan

**ANTIBIOTICS**

**DOXORUBICIN**

* One of the most important anticancer drugs with major clinical activity in several cancers
  + included in almost half of drug combinations
* Intercalates with DNA bases and inhibits DNA and RNA  polymerases
* Produces severe alopecia
* A potent vesicant
* TOXICITIES: **CARDIOTOXICITY**
  + ACUTE: Arrhythmias
  + CHRONIC: Digitalis-resistant congestive heart failure;  lifetime dose dependent - 20% of patients receiving 550 mg/m2
    - damage from radicals
  + PROTECTION AGAINST DOXORUBICIN-INDUCED CONGESTIVE HEART FAILURE

Combines with doxorubicin to generate reactive oxygen

* protective chelater. protects vs cardiotoxicity induced by doxorubicin
  + Dexrazoxane🡪metalkelating metabolite. fx to prevent free radical damage by taking them up

**DACTINOMYCIN**

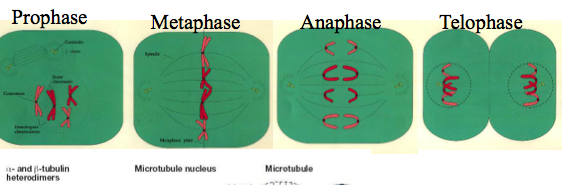
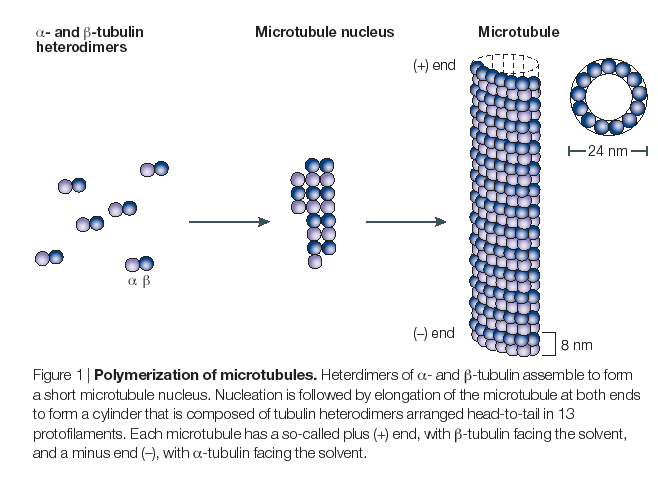
* IV tx
* is isolated from soil bacteria of the genus *Streptomyces*.
* It was the first antibiotic shown to have anti-cancer activity
  + Still used for the treatment of acute myeloid leukemia
* It inhibits transcription by binding to DNA at the transcription initiation complex and preventing elongation by RNA polymerase.
* it also binds DNA duplexes and interferes with DNA replication

**BLEOMYCIN**

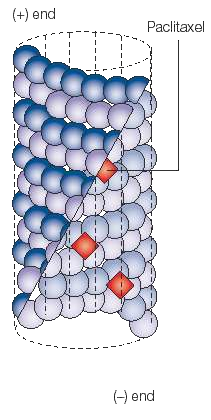
* Is a small peptide that contains a DNA- binding region and an iron-binding domain at opposite ends of the molecule.
* It acts by binding DNA, which results in single-strand and double-strand breaks following free radical formation (superoxide and hydroxyl radicals), and inhibition of DNA biosynthesis
* It is cytotoxic in any phase of the cycle even on G0 phase
* Uses
  + Bleomycin is used in the treatment of a number of different cancers, including cancer of the head and neck, skin, esophagus, lung, testis, and genitourinary tract.
  + In addition, it is used in the treatment of Hodgkin's disease and non−Hodgkin's lymphomas.
* Side effects
  + Pulmonary fibrosis\*, like busulfan
  + Raynaud's phenomenon (which affects the fingers and toes, may involve pain, pale color, and abnormal sensation as burning)
  + In addition, headache, and nausea and vomiting may occur.

**MITOTIC SPINDLE POISONS**

**VINCA ALKALOIDS**

* **** ****
* The vinca alkaloids
  + Vincristine & vinblastine (M-phase)
  + Binds to microtubules - Supression of microtubuli dynamics- Metaphase arrest
  + Depolymerization of microtubules at high conc.
* Mitosis
* 
* 
  + Antimitotic agents bind to microtubules
  + **Metaphase arrest**
* Vinca Alkaloids, Vinblastine and Vincristine prevent assembly of mitotic microtubules
* *Tubulin* is a structural protein which polymerizes to form microtubules.
* The cell cytoskeleton and mitotic spindle are made of microtubules.
* *Vincristine* binds to tubulin inhibiting polymerization of microtubule structures.
* Disruption of the microtubules arrests mitosis in metaphase.
* The vinca alkaloids therefore affect all rapidly  dividing cell types including cancer cells, but also intestinal epithelium and bone
  + bone marrow suppression common
* Uses
  + breast cancer, testicular cancer, lymphomas, neuroblastoma, Hodgkin's and non-Hodgkin's lymphomas
* Side effects
  + The main side-effects of **vincristine are peripheral  neuropathy and bone marrow suppression.**
    - no periph neuropathy w/ just vincristine
  + Accidental injection of vinca alkaloids into the spinal canal (intrathecal administration) is highly dangerous, with a mortality rate approaching 100%. (vinblastin is less neurotoxic)

**PACLITAXEL**

* hyper-stabilizes microtubule structure (freezes them).
* 
* Paclitaxel binds to the β subunit of tubulin ,the resulting microtubule/paclitaxel complex does not have the ability to disassemble.
* This adversely affects cell function because the shortening and lengthening of microtubules is necessary for their function.
* Resulting in apoptosis of cancer cells.
* Uses
  + in the treatment of lung and breast cancer .
  + used in cisplatin-resistant ovarian cancer
* Side effects
  + Bone marrow suppression and neurotoxicity
  + hypersensitivity in 1-2% of patients: pre- treat with antihistamines and steroids

**EPIPODOPHYLLOTOXINS**

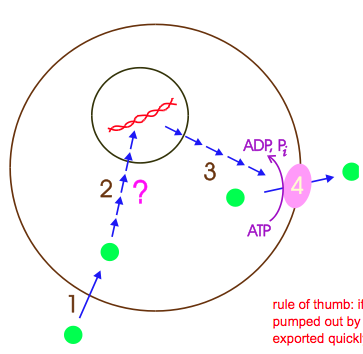
**ETOPOSIDE**

* It has been useful for treatment of germ cell cancer, small cell and non-small cell lung cancer, Hodgkin’s and non-Hodgkins lymphomas, and gastric cancer.
* MOA:
  + DNA scission (Topoisomerase II inhibitor)
* Inhibition of topoisomerase II, which results in DNA damage through strand breakage induced by the formation of a ternary complex of drug
* Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, and lead to cell death. Etoposide acts primarily in the G2 and S phases of the cell cycle.

**CAMPTOTHECINS**

* Topotecan and Irinotecan
  + Inhibit the activity of topoisomerase I, the key enzyme repsonsible for cutting and religating singe DNA strands.
  + Resulting in DNA damage.
  + Used for advanced ovarian cancer as second-line thearpy following initial treament with plantinum- based chemo
  + Used in combination with 5-FU and leucovorin in metastatic colorectal cancer
  + Immediate and delayed diarrhea – the latter can be severe and may lead to electrolyte imbalance and dehydration

**DEVELOPMENT OF MULTIPLE DRUG RESISTANCE**

1. Uptake of drug
2. Signal transduction to nucleus
3. Expression and processing of drug pump
4. Mature MDR-1 pump eliminates a broad spectrum of antineoplastics
   * rule of thumb: if natural products typically pumped out by MDR eg vinca alkyloids exported quickly bc natural product
   * 

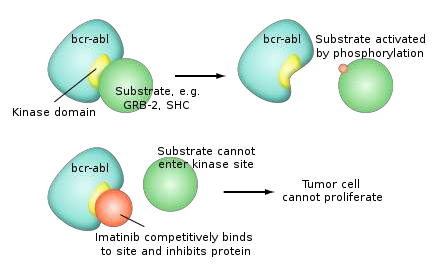
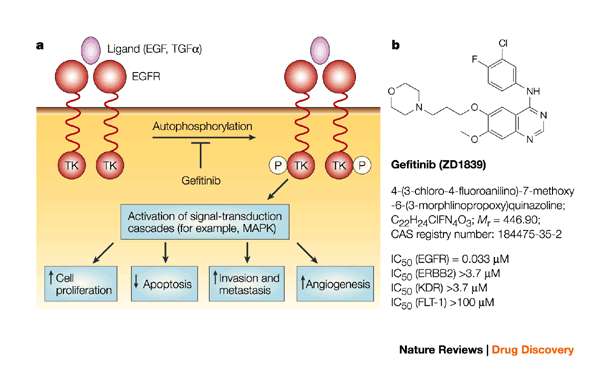
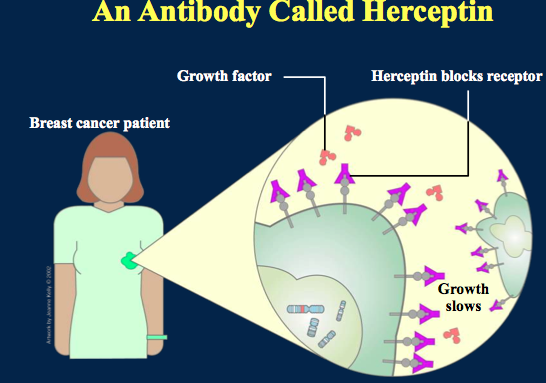
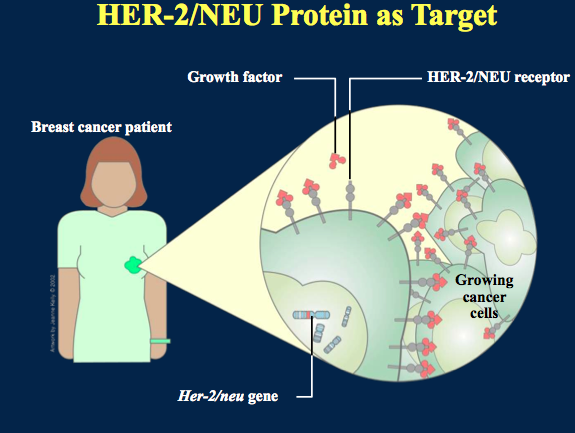
**ANTINEOPLASTIC DRUGS HORMONAL AGENTS**

* Endocrine therapy:
  + Many hormonal antitumor agents are functional agonist or antagonist of the steroid hormone family.
  + Adrenocorticoids
  + Androgens
  + Estrogens
  + Progestins
  + Aromatase inhibitors
  + Gonadotropin-releasing hormone agonists (GnRH)
  + Luteinizing hormone-releasing hormone (LHRH)
* **Corticosteroids**
  + Corticosteroids have broad use in cancer treatment. Some are used to treat adult leukemias, adult lymphomas, and acute childhood leukemia.
    - good at inhib NFKB in immune cells
  + Immunosuppressive mechanism
    - Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines interleukin and TNF-γ, the most important of which is the IL-2. The inhibition of cytokine production reduces T cell proliferation and induces apoptosis.
      * IL2 induced by NFKB
  + The most common corticosteroids used in cancer treatment are:
    - dexamethasone (Decadron)
    - Hydrocortisone
    - methylprednisolone (Medrol)
  + Side effects
    - Hyperglycemia due to increased gluconeogenesis, insulin resistance caution in those with diabetes mellitus
    - reduced bone density (osteoporosis, higher fracture risk, slower fracture repair)
    - weight gain due to increased visceral and truncal fat deposition (central obesity) and appetite stimulation
    - adrenal insufficiency (if used for long time and stopped suddenly without a taper)
      * affects something at hypothalamus. unintelligible on recording PMC
    - muscle breakdown (proteolysis), weakness; reduced muscle mass and repair
      * develop fatty liver long term short term break down fat
* **Tamoxifen (hormone antagonists)**
  + Tamoxifen selectively inhibits the effects of estrogen on breast tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density) and uterine tissues.
    - An estrogen receptor (ER) antagonist
      * ER+ can use tamoxifen
      * ER- do not
    - Only useful in cancers expressing ER or progesterone receptor (PR)
  + These qualities make tamoxifen an excellent therapeutic agent against breast cancer.
  + It is known to compete with estrogen by binding to estrogen receptors in target cells, thus limiting the effects of estrogen on breast tissue.
  + Adverse Effects
    - CNS: Depression, light headedness, dizziness, headache, decreased visual acuity &retinopathy
    - Hematological: Hypercalcemia
    - GU: *Vaginal bleeding, vaginal discharge & menstrual irregularities*
    - Dermatologic: *Hot flashes, skin rash*
* **Aminoglutethimide**
  + Aminoglutethimide inhibits the enzymatic conversion of cholesterol to D5-pregnenolone, resulting in a decrease in the production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens.
  + It has been used in the treatment of advanced breast and prostate cancer.
* **Anastrozole**
  + aromatase inhibitor
  + Anastrozole is a drug indicated in the treatment of breast cancer in post-menopausal women.
  + It is used both in adjuvant therapy (i.e. following surgery) and in metastatic breast cancer.
  + It decreases the amount of estrogens that the body makes.
  + Anastrozole belongs in the class of drugs known as aromatase inhibitors. It inhibits the enzyme aromatase, which is responsible for converting androgens (produced by women in the adrenal glands) to estrogens.
* **GNRH ANALOGUES**
  + Goserelin Acetate
    - Goserelin acetate is a synthetic hormone that acts similarly to the naturally occurring gonadotropin−releasing hormone (GnRH). In men, this results in decreased blood levels of the testosterone. In women, it decreases blood levels of estrogen.
    - It is used for treatment of breast (women) and prostate (men) cancer
    - Side effects
      * sweating ,hot flashes, impotence (erectile dysfunction) and sterility
      * depression or other mood changes
      * Other common side effects in women include: light, irregular, vaginal bleeding & no menstrual period
  + Antiandrogens
    - tumors initially androgen sensitive and become insens later on
    - Flutamide: an antiandrogen that effectively blocks the binding of androgen to its receptor in the peripheral tissue.
    - It is used in the treatment prostate cancer
    - Leuprolide: GnRH and LHRH agonist
      * Initially stimulates secretion of testosterone, but later prevents it
      * Combined with flutamide to treat prostate cancer

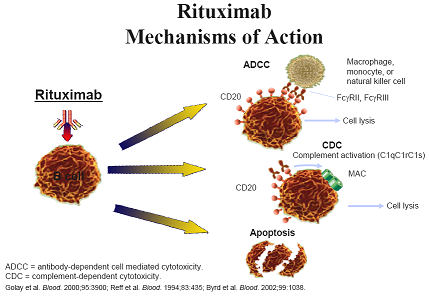
**ANTINEOPLASTIC DRUGS--NEWER DRUGS THAT TARGET SIGNAL TRANSDUCTION PATHWAYS**

* Receptor Tyrosine Kinase Inhibitors
* Proteasome inhibitor (Bortezomib)
* Humanized Mouse Monoclonal Antibodies

**RECEPTOR TYROSINE KINASE INHIBITORS**

* Imatinib Mesylate (Gleevec®)
  + Inhibitor of BCR/ABL🡪the constitutively activated tyrosine kinase produced by chromosome translocation in CML
  + Blocks white blood cell proliferation
  + 
* Gefitinib (Iressa®) for Non-Small Cell Lung Cancer (NSCLC)
  + Gefitinib binds to EGF receptor (EGFR) and inhibits it.
    - so inhib downstream effects as well
  + 
* BORTEZOMIB (Velcade®)
  + An inhibitor of the proteasome: the major protein metabolizing enzyme in cells
  + Proteasome regulates cell cycle progression by controlling entry into the major phases of the cell cycle.
  + Build-up of damaged proteins because of proteasome inhibition results in cell death.
  + FDA approved for treatment of multiple myeloma
  + 

**MONOCLONAL ANTIBODY THERAPY: TRASTUZUMAB (HERCEPTIN®): A HER2 RECEPTOR ANTIBODY**

* The HER2 receptor is expressed in about 30% of breast cancer patients, and is associated with rapid progression.
* Trastuzumab binds to HER2 and inhibits its growth signaling properties.
* ADVERSE EFFECTS:
  + 1. Severe allergic reactions.
  + 2. Cardiomyopathy when co-administered with doxorubicin or cyclophosphamide: There is some evidence that administration of trastuzumab too soon after cessation of doxorubicin prevents heart muscle fiber recovery. HER2 receptor is upregulated after heart damage & is thought to be important for recovery from cell wounding.
* Rituximab (Rituxan®): Treatment of non-Hodgkins lymphoma
  + Targets CD20 in B-lymphocytes
  + Severe reactions may occur including anaphylaxis.
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* Cetuximab (Erbitux®): EGFR- expressing metastatic colorectal carcinoma
  + Can cause hypotension and pharyngeal edema on infusion
  + Pulmonary inflammation and scarring
  + Skin rashes, especially when exposed to sunlight